

# **WILSON'S DISEASE IN ONE IDENTICAL TWIN AND TREATMENT BY TRIETHYLENE TETRAMINE 2HCl IN ANOTHER CASE**

by

**R. G. PETER WATSON, BSc, MRCP, (UK)**

Department of Neurology, Royal Victoria Hospital, Belfast

WILSON'S disease is a rare genetic condition associated with excess copper deposition in the tissues, principally liver and brain. It first became established as a clinical entity in 1912, following Kinnear Wilson's publication of thirteen cases.<sup>1</sup> The incidence has been estimated to be about one case per million of the population<sup>2</sup> although Walshe<sup>3</sup> considers it is likely to be more common than this. Since it is a condition which can be effectively treated, early diagnosis is essential.<sup>3, 4</sup>

In the space of six months, two cases with contrasting features have presented to the Department of Neurology.

## **CASE 1 AG AGED 17 MALE**

In 1979 this patient, one of identical twin brothers, joined the army, but disliked it and left after serving only three months. He then worked in a butcher's shop but left six months later, at the end of 1979, when he lost interest in this too. His family noticed that he had become less sociable and he slept a great deal. By the summer of 1980 he had developed a peculiar nodding action of his head and he had become so withdrawn that medical help was sought. A possible diagnosis of schizophrenia was considered and he was admitted for psychiatric care.

Over the next four months, he remained withdrawn and he developed slurred speech and unsteadiness of walking. From December, 1980 to March, 1981 his condition deteriorated rapidly with severe difficulty speaking and swallowing, and increasing limb stiffness. By this time he was unable to walk and could not feed himself.

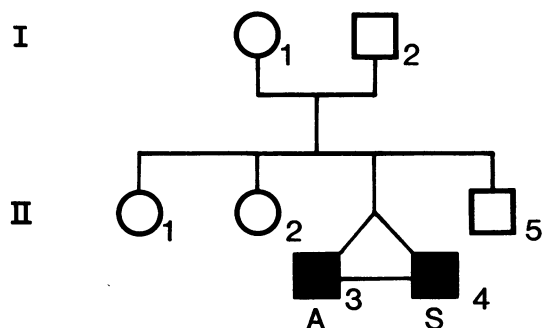
On admission to the Neurology Unit he had a totally immobile face, was unable to speak and had great difficulty in swallowing. There were no involuntary movements, but the limbs showed a severe degree of rigidity.

On examination of the eyes characteristic Kayser-Fleischer rings were found and a confident diagnosis of Wilson's disease was made. This was confirmed by the biochemical findings of low serum copper, low serum caeruloplasmin and raised urinary copper clearance (Table 1). Liver function tests were normal apart from a marginally elevated alkaline phosphatase to 149 u/l (normal 35-105). Liver biopsy showed a marked increase in fibrous tissue and some nodular degeneration. The copper content of this tissue was not estimated.

The family tree is shown in Fig. 1. A feature of particular interest is the occurrence of this condition in one of identical twins. Confirmation of identical genotypes was obtained by a detailed comparison of blood groups (Table 2). The brother showed no clinical evidence of the disease. His biochemical findings (II<sup>4</sup>) and those of the rest of the family are shown in Table 1.

Fig 1

Family Tree of Case 1



	NORMAL	I <sup>1</sup>	I <sup>2</sup>	II <sup>1</sup> 34 yrs	II <sup>2</sup> 24 yrs	II <sup>3</sup> 17 yrs	II <sup>4</sup> 17 yrs	II <sup>5</sup> 13 yrs
SERUM COPPER	13 - 26 $\mu\text{mol/l}$	17	10 ↓	22	10	3 ↓	2 ↓	12 ↓
SERUM CAERULOPLASMIN	0.27 - 0.63 g/l	0.27	0.17 ↓	0.38	0.17 ↓	<0.09 ↓	0.04 ↓	0.18 ↓
URINARY COPPER CLEARANCE	0.2 - 1.6 $\mu\text{mol/24 hrs}$	1.5	1.5	1.8 ↑	1.8 ↑	3 ↑	1.1	1.6

● PATIENT AG  
↑ ABOVE NORMAL RANGE  
↓ BELOW NORMAL RANGE

TABLE 1. BIOCHEMICAL PARAMETERS FOR FAMILY OF CASE 1.

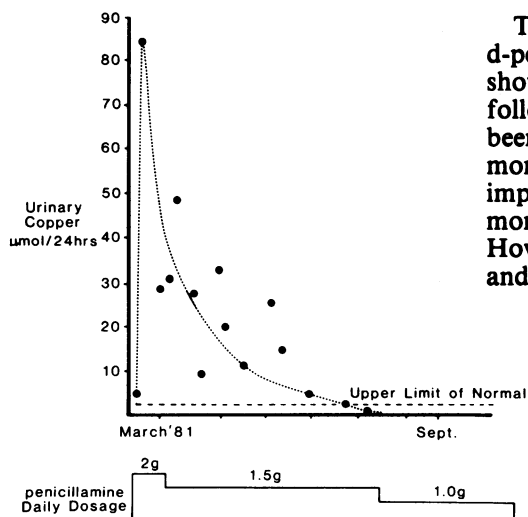


Fig 2 Effect on urinary copper clearance by penicillamine in Case 1

Treatment was commenced with d-penicillamine, 2 grams daily. Fig. 2 shows the increased clearance of copper following treatment. Clinical response has been disappointing. During the first three months of treatment there was some improvement in swallowing and after 18 months he is able to walk with help. However, he remains severely disabled and still unable to speak.

#### CASE 2 BM AGED 24 FEMALE

This young woman, who works as a clerk, presented with a history of unsteadiness on her feet and frequent falls, over a period of six months. The unsteadiness had become gradually worse and she had also experienced difficulty with writing, and drinking from a cup, because of shaking hands.

NAME	ABO	Rh Geno	K	k	Fy <sup>a</sup>	Fy <sup>b</sup>	JK <sup>a</sup>	JK <sup>b</sup>	Le <sup>a</sup>	Le <sup>b</sup>	M	N	S	s	P <sub>1</sub>
AG	O	R <sub>1</sub> r CDe/cde	-	+	-	+	+	+	+	-	-	+	-	+	+
SG	O	R <sub>1</sub> r CDe/cde	-	+	-	+	+	+	+	-	-	+	-	+	+

TABLE 2. COMPARISON OF BLOOD GROUPS IN TWINS

On examination, she was euphoric and had a variable coarse tremor of the upper limbs at rest. It was made worse by voluntary movement and tended to become quite violent at times of excitement. She is right handed and this side was more severely affected. Tone was normal and there was no weakness. Her gait was ataxic and at times this became so severe that she almost fell. There was no nystagmus.

Initially a diagnosis of multiple sclerosis was considered likely, but examination of the eyes again showed the diagnostic Kayser-Fleischer rings of Wilson's disease. Biochemical screening confirmed the abnormal copper metabolism. She has three siblings, none are affected clinically.

Treatment was started with d-penicillamine 2 grams daily. There was a good biochemical response (Fig. 3) and clinically her condition also improved. However, following discharge from hospital compliance was poor despite reduction of dosage to 500 mg daily. She developed nausea and a skin rash, and had one episode of jaundice, probably haemolytic type (this occurred while she was at home and confirmatory tests were not obtained).

Her clinical condition had deteriorated markedly by the end of 1981 and a further attempt was made to achieve a therapeutic dose of penicillamine using steroid cover. Unfortunately side effects, particularly nausea proved again troublesome and the drug had to be abandoned.

In February, 1982 triethylene tetramine dihydrochloride (Trien) was introduced at a dose of 600 mg daily increasing to 1500 mg daily and this has been successful in maintaining a good urinary copper clearance (Fig. 3) with good tolerance. Her clinical condition also improved as shown by her writing and drawing. Unfortunately this patient's compliance with drug therapy has again been suspect and the case continues to cause problems in management.

## DISCUSSION

These two cases clearly demonstrate the variety of clinical manifestations of neurological Wilson's disease and the difficulty which the diagnosis may present. The importance of the diagnostic sign of Kayser-Fleischer rings cannot be over emphasised and these should be carefully looked for by slit lamp examination if necessary, in any unusual neurological syndrome in young people. Wilson's concept of progressive lenticular degeneration is now recognised as too narrow since copper is deposited throughout the brain including the cerebellum and cerebral cortex, and not just in the basal ganglia.<sup>5</sup> Damage can occur at any of these sites and give rise to a variety of clinical manifestations. Walshe<sup>3</sup> stresses this point and lists the

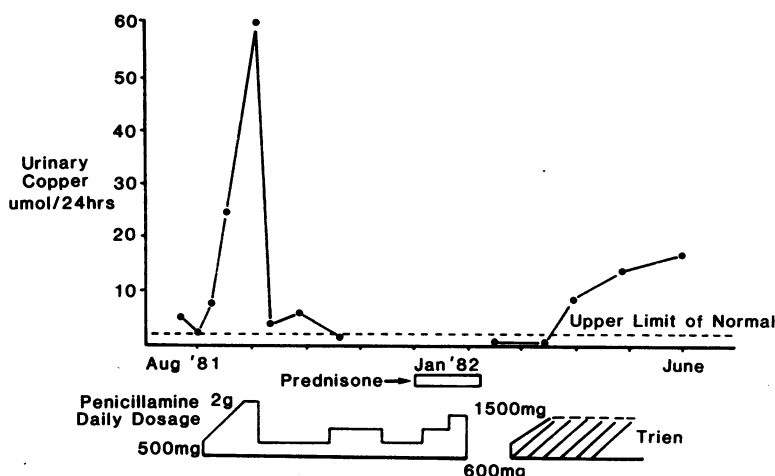


Fig 3 Effects on urinary copper clearance by penicillamine and then triethylene tetramine in treatment of Case 2

following features which have been documented in neurological Wilson's disease; tremor, which may be of the Parkinsonian or intention variety, ataxia, rigidity, drooling, dysphagia, behaviour disorders, in particular euphoria and intellectual impairment, and seizures are also occasionally seen. A useful maxim is that no two cases of neurological Wilson's disease are entirely alike.

In retrospect our first case most closely fitted the classical text book description of an extra pyramidal, Parkinsonian-like syndrome, but initially it was the behavioural disorder rather than any physical problem which caused diagnostic confusion. In the second case the presenting features were largely those of a cerebellar disorder.

The ages of our two patients were 17 and 24 years, consistent with Walshe's<sup>3</sup> average age of presentation in his series as 18.9 (range 5-40). Cases with a predominantly hepatic presentation tend to be younger (average age 11.4 years).

Since the disease is inherited as an autosomal recessive trait, it is imperative to screen siblings for early clinical features and biochemical abnormalities, a point dramatically illustrated in Case 1, where an identical twin was asymptomatic. He is now being treated prophylactically with 1 gram of penicillamine daily. We are aware of no other published instances of identical twins with Wilson's disease but J. M. Walshe knows of two unpublished cases (personal communication). It is perhaps surprising that the twins should have been affected to such a different degree. This must be environmentally determined and most obviously suggests a difference in dietary copper intake. The boys were brought up together and have never been apart, including a short period when they were both in the army. Their eating habits have always been similar, but for a period of at least eighteen months, A. G. drank a large amount of Coca Cola each day. His brother drank relatively little. Each can of Coca Cola contains 0.1 mg. of copper.<sup>6</sup> The average daily intake of dietary copper is 2-5 mg.<sup>7</sup> If A. G. consumed five or six cans of Coca Cola daily (his reported

average) this could represent a 10-25 per cent increase in copper intake compared to his brother and may have been the crucial environmental difference.

It is of note that heterozygote carriers show biochemical changes in the same direction as affected individuals but usually to a less marked degree.<sup>3</sup> This is seen in Table 1 where A. G.'s parents, who must be heterozygotes, have mildly abnormal or borderline normal values. The siblings, other than his twin, have at least one mildly abnormal change and may be heterozygotes. The ranges of biochemical values for affected individuals and heterozygotes are so wide that they can over-lap and this sometimes makes it difficult to differentiate between an affected presymptomatic individual who needs treatment and a carrier who does not.

Walshe suggests that in such cases a liver biopsy should be carried out for histological examination and copper estimation. However, the latter is difficult with a small amount of biopsy material and histochemical methods have often been found to be unreliable.<sup>8</sup> It was also our experience with the liver biopsy from Case 2 that several histochemical techniques failed to demonstrate copper despite characteristic histological changes both by light and electron microscopy.

Treatment is designed to promote the mobilization and excretion of excess copper deposited in the tissues. The drug of choice is d-penicillamine, a chelating agent introduced in 1956.<sup>9</sup> The clinical results can be very rewarding provided treatment is not delayed until neurological damage is irreversible. This is presumably the situation in our first case, although improvement may sometimes be delayed for a year or more after the initiation of treatment.<sup>3</sup> Toxic reactions to penicillamine are not uncommon; these include urticaria and other skin rashes, nausea, anorexia, vomiting, fever, thrombocytopenia with or without leucopenia and a collagen disease-like reaction. Other less common signs of toxicity are mouth ulceration, pyridoxine deficiency, skin fragility, nephrotic syndrome, haemolytic anaemia and Goodpasture's syndrome.

Fortunately a newer drug, triethylene tetramine dihydrochloride (Trien) was introduced in 1969<sup>10</sup> and has been shown to be an equally effective chelating agent although acting in a slightly different way.<sup>11</sup> Certainly in Case 2 the effect of the preparation in producing copper excretion was excellent (Fig. 3) and recent authors<sup>12, 13</sup> report continued effectiveness and safety with long term administration.

The drug has only recently become commercially available (1978) and has not been subject to formal toxicity testing. Trien has therefore not yet been approved by any national committee. However, it remains the only practical alternative drug to penicillamine in this disease and has proved biochemically and clinically effective in this case.

## SUMMARY

The clinical presentation, investigation and management of two recent cases of neurological Wilson's disease are described. Various aspects of the disorder are discussed and the variety of clinical presentation emphasised.

The first case occurred in only one of monozygotic twins and a possible explanation for this is considered. In the second patient serious side effects resulted from the use of penicillamine, and a new drug triethylene tetramine dihydrochloride (Trien) was successfully used as an alternative chelating agent.

### ACKNOWLEDGEMENT

I am grateful to Dr. M. Swallow for his permission to report these cases and for his generous help and advice.

### REFERENCES

- 1 Wilson SAK. Progressive lenticular degeneration; a familial nervous disease associated with cirrhosis of the liver. *Brain* 1911/12; 34: 259-509.
- 2 Bearn AG. Wilson's disease. An inborn error of metabolism with multiple manifestations. *Am J Med* 1957; 22: 747-757.
- 3 Walshe JM. Wilson's Disease. In: Viken PJ, Bruyan GW, eds. *Handbook of Clinical Neurology* 27. North-Holland Pub Co; 1976: 379-414.
- 4 Anonymous. Don't forget Wilson's disease (editorial) *Br Med J* 1978; 2: 1384-5.
- 5 Warren PJ, Earl CJ, Thompson RHS. The distribution of copper in human brain. *Brain* 1960; 83: 709-717.
- 6 Paul AA, Southgate DAT. *McCaine and Widdowson's. The Composition of Foods*. 4th ed. Ministry of Agriculture, Fisheries and Food; MRC, 1978: 251.
- 7 Schienberg IH, Sternlieb I. Copper Metabolism *Pharmacol Rev* 1960; 12: 355-381.
- 8 Lindquist RR. Studies on the pathogenesis of hepatolenticular degeneration, cytochemical methods for the localization of copper. *Arch Path* 1969; 87: 370-379.
- 9 Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Amer J Med* 1956; 21: 487.
- 10 Walshe JM. Management of penicillamine nephropathy in Wilson's disease, a new chelating agent. *Lancet* 1969; 2: 1401.
- 11 Walshe JM. Copper chelation in patients with Wilson's disease, a comparison of penicillamine and triethylene tetramine dihydrochloride. *Quart J Med* 1973; 42: 441-52.
- 12 Walshe JM. The management of Wilson's disease with triethylene tetramine 2 HCL (Trien 2 HCL) *Prog Clin Bio Res* 1979; 34: 271-80.
- 13 Haslam RHA, Sass-Kortsah A, Stout W, Berg M. Treatment of Wilson's disease with triethylene tetramine dihydrochloride. *Develop Pharmacol Therap* 1980; 1: 318-24.